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SPECIAL ISSUE

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Reviewers Find A Trial That Never Ends With 90% of Consent Forms Unobtainable

By Paul Goldberg

Radiologist Claudia Henschke and Weill Cornell Medical College forged a business partnership that started in 1991 and ended abruptly in 2009.

Henschke and her colleagues developed and patented technologies for using computed tomography to screen current and former smokers for early-stage lung cancer. Weill Cornell had a stake in this growing portfolio of intellectual property.

These inventions offered more than promises of money. The money was real: innovations generated royalties from General Electric, the maker of CT scanners.

On the patient care side, high-profile promotion of screening attracted new patients, giving the institution an advantage in New York's hyper-competitive health care market.

Researchers received millions of dollars in grants from the federal government, New York City, private foundations and the Liggett Group, a tobacco company. Weill Cornell took a cut.

There was publicity, too, including gushing network news pieces about

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Guest Editorial:

"What Purpose is Served by Accruing More Subjects?" I-ELCAP Confidential Documents Stun Veteran Auditor

By Raymond Weiss

At the request of the editor of The Cancer Letter, I reviewed the Oct. 7, 2008, report of the four-member independent scientific review committee convened by Weill Cornell to assess the research of the International Early Lung Cancer Action Program.

The screening program began in 1992, was greatly expanded in 2001, and expanded again in 2003. It received federal funding, including two R01 grants (R01-CA-63393 and R01-CA-78905) and one U01 grant (U01-CA-091100). At the time it was reviewed by the outside experts, the study involved 38 centers in several countries, recruiting over 40,000 subjects.

In terms of accrual, this project exceeds the size of some of the well-established, NCI-funded clinical trials cooperative groups. The project continues to accrue subjects, even though a number of questions have been raised—questions regarding the scientific construct of the study, and its conduct relative to subject consent and IRB oversight.

These questions resulted in the review committee evaluation at Weill

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Henschke:Study Got No NCI Money, Federal Protections Don't Apply

(Continued from page 1)

people whose lives were purportedly saved by early detection. Publicity is an intangible, but it's prized nonetheless. Henschke generated it by the barrelful.

When the partnership dissolved with no explanation to the outside world, many oncology insiders were left wondering. Did other institutions make a better offer?

Internal Weill Cornell documents obtained by The Cancer Letter and The New York Times show that, until 2008, the Henschke group, called the International Early Lung Cancer Action Program, or I-ELCAP, operated without significant institutional oversight.

Scrutiny by Weill Cornell began when the American Cancer Society and at least one journal editor called for an audit of the screening group's data. This was in part because of press reports of undisclosed conflicts of interest on the part of the Henschke group and in part because other scientists questioned the reliability of the group's findings.

"Given the global reach of this program, its potential for advancing the state of the art in early lung cancer detection and treatment, and its potential economic and political impact, it is surprising that the WCMC administration has avoided direct oversight of this program, especially knowing that scientific controversy has surrounded I-ELCAP almost from its inception," the four-member review committee wrote in its report to Weill Cornell.

The document was stamped "confidential" and was not intended to be released.

The partnership between the researchers and the institution dissolved in silence.

Weill Cornell dropped out of the screening program it once housed and its name disappeared from the I-ELCAP website. The I-ELCAP leaders—Henschke and collaborator David Yankelevitz—departed to take dual appointments at the Mt. Sinai Medical Center and the Arizona State University BioDesign Institute. The I-ELCAP operations center moved from Weill Cornell to Arizona.

The timeline of this controversy appears on the next page of this issue.

Internal documents show that the review committee members hired by Weill Cornell were stunned to find that the study, which by that time had enrolled 40,000 volunteers, lacked standard protection for research subjects.

I-ELCAP's top leaders were either unable to provide consent documents for 90 percent of the participants or declined to do so. Moreover, the four outside reviewers noted that the design of the study was such that there would be no way to know when the hypothesis had been proven or disproven.

The study could continue indefinitely.

The reviewers urged that recruitment to the experiment be stopped and institutions that continued to enroll participants be notified.

Yet, to this day, the I-ELCAP study continues to accrue patients, and there is no evidence that any researchers have been notified by Weill Cornell of the findings of the external reviewer committee.

Similarly, there is no evidence that government agencies, which protect patients from unreasonable risks, or editors of journals that have published—and continue to publish—I-ELCAP papers received any notification.

The Cancer Letter asked Raymond Weiss, former auditor at Cancer and Leukemia Group B, who has conducted 2,200 audits of clinical trials, and whose work exposed fraud in the high-dose chemotherapy and bone marrow transplantation study by the South African researcher Werner Bezwoda, to review the Weill Cornell internal documents.

"If healthy people are still being enrolled, without the establishment of… [a data and safety monitoring board], that is a major deviation from standard procedures," Weiss wrote after reviewing documents.

Weiss's commentary appears on page 1.

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Henschke said I-ELCAP shouldn't be held to the same standards as cooperative groups, because it's not a cooperative group, and it had never received federal funds for clinical studies.

"The idea that we need to act as if we are an NCI cooperative cancer network that focuses on federally funded randomized treatment trials reflects a lack of understanding of non-federally funded research," she said in an email responding to questions from The Times and The Cancer Letter. "I-ELCAP never had the responsibility of obtaining consents from participating patients."

In another email, Henschke said this has been the case from the outset. "I-ELCAP was conceived as a prospective pooling program rather than performing a meta-analysis after various studies are done," she wrote. "The responsibility for obtaining consents rested with the individual researchers at each of the collaborating sites. The individual sites validated the consents had been obtained and that all the requirements of the I-ELCAP IRB were met."

Henschke's entire response appears in p. 16. The Times story is available at: http://nyti.ms/lCd7qP.

The absence of notification is significant because medical journals require proper informed consent in clinical experiments. Papers that don't have proper consent can't be published in journals that agree to these standards.

The rules of an organization of premier medical journals state that retractions should be considered when editors believe that they published "unethical research." The rules are posted at http://publicationethics.org/files/u661/Retractions_COPE_gline_final_3_Sept_09__2_.pdf

The papers submitted by I-ELCAP had to rely on representations of the investigators that consent had been obtained, Henschke said,

"All site investigators were responsible for obtaining the consents locally and for following their local IRB process," she said. "We followed all the processes required by the IRB for the pooling effort and for its reporting. Our only requirement is to rely on their representation."

If it's true that consent cannot be documented, as the review committee report states and as Henschke readily acknowledges, the volume of retractions could be record-setting. PubMed lists 135 papers co-authored by Henschke and Yankelevitz.

Just as importantly, Weill Cornell had an "assurance" with the federal government that research on human subjects would be conducted with proper safeguards, regardless of whether it is funded by the government or private entities. The terms of assurance are posted at http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html

Federal guidelines that apply are posted at http://ohsr.od.nih.gov/guidelines/45cfr46.html#46.117.

Henschke said the Weill Cornell IRB didn't oversee the I-ELCAP operations center.

"Some of the collaborating institutions received federal funding for their screening research," she said in an email. "They voluntarily contribute to I-ELCAP and are free to publish the results from their

The I-ELCAP Timeline

1992

A group of physicians from Cornell University Medical Center join doctors from other institutions to study helical CT imaging.

They call their project the Early Lung Cancer Action Program, ELCAP. It's headed by radiologists Claudia Henschke and David Yankelevitz.

July 10, 1999

The Lancet publishes an ELCAP paper comparing CT scans and chest X-rays in 1,000 symptom-free volunteers, aged 60 years or older, with at least 10 pack-years of cigarette smoking.

The study focuses on sensitivity. Non-calcified nodules were detected in 23 percent of participants by low-dose CT at baseline, compared with 7 percent by chest radiography.

Malignant disease was detected in 27 patients by CT, versus seven by chest X-ray. The paper is posted at: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(99)06093-6/abstract

Henschke and her supporters equate sensitivity with survival, arguing that CT screening can increase survival in lung cancer to 80 percent.

"We're saying that we could change survival from 12 or 15 percent to 80 percent," said Henschke tells to The New York Times. "There are 172,000 new cases a year. Think of 12 percent or 15 percent survival, compared to 80 percent." The Times story: http://nyti.ms/mx9ntA.

April 11, 2000

Henschke and Yankelevitz notify the U.S. Patent and Trademark Office

projects independently. These federally funded grants were grants for specific screening projects, each with their own IRB, not for the pooling of the data which has its own IRB approval. I-ELCAP functioned with its own separate and distinct IRB, distinct from the individual screening site IRBs. I-ELCAP is also distinct from the Weill Cornell screening IRB (ELCAP which ended in January 2009)."

Documents show that federal grants obtained by I-ELCAP researchers at Weill Cornell included two NCI R01 grants, one NCI U01 grant, and one NCI R41 grant. The group also obtained three HHS grants.

Meanwhile, I-ELCAP member institutions continue to accrue participants to the study.

A publication by Henschke's and Yankelevitz's new employer—the Arizona State University Biodesign Institute—states that the number of participants is up to 53,000. http://www.biodesign.asu.edu/news/study-supports-asu-biodesign-institute-researchers-pioneering-work-on-the-use-of-ct-scans-for-the-early-detection-of-lung-cancer

John Rogers, the chief spokesman for Henschke's former employer, Weill Cornell, didn't acknowledge repeated efforts by The Cancer Letter to reach him through his staff members and email. The Biodesign Institute didn't respond to questions from The Cancer Letter.

The Review Committee Describes Fundamental Problems

The review committee hired by Weill Cornell in the fall of 2008 was headed by Geoffrey Rubin, then-chief of cardiovascular imaging in Stanford University's Department of Radiology, who has since become chair of the Department of Radiology at Duke University.

Group members were:

• David Carbone, the Harold L. Moses Chair in Cancer Research and director of Specialized Program of Research Excellence in Lung Cancer at Vanderbilt-Ingram Cancer Center,

• Lawrence Goodman, professor of radiology and chief of thoracic imaging at the Medical College of Wisconsin, and

• Steven Piantadosi, director at the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai Medical Center.

Weill Cornell paid the reviewers $10,000 each, and all were asked to sign non-disclosure agreements.

In the report, the committee catalogued fundamental problems, which ultimately led them to question whether the trials, which at that time enrolled over 40,000 people, were being conducted ethically.

The committee's findings include:

• No sample size calculation for the group's single-arm study had been done. This means that at the outset of the study, the researchers had no idea how many patients would have to be screened to test the hypothesis.

• The group of researchers who conducted the clinical experiment was not supervised by the institution, either for ethics or validity of science. Given its global reach, "it is surprising that the WCMC administration has avoided direct oversight of this program."

• I-ELCAP leaders acknowledged that they were able to locate

that they are about to file a patent application for screening technology. This application—which lists Cornell as the "assignee"—is the first in a series of technologies which generate royalties for the institution and inventors (The Cancer Letter, Jan. 18, 2008).

Aug. 21, 2000

Then-Mayor Rudolph Giuliani announces the formation of the New York Early Lung Cancer Action Program, to "help develop the best means for early detection and successful treatment of lung cancer."

The initiative uses funds from the New York Tobacco Settlement fund to pay for 10,000 past or present heavy smokers to get CT scans. A Viewpoint article in The Lancet is posted at: http://www.vaoutcomes.org/papers/Tobacco.pdf

Dec. 4, 2000

Vector Group Ltd., parent of the Liggett Group Inc. tobacco company, gives Henschke's group $2.4 million.

Altogether, Liggett contributes $3.6 million to the Henschke group, and the money is placed in the Foundation for Lung Cancer: Early Detection, Prevention & Treatment (http://www.sourcewatch.org/index.php?title=Foundation_for_Lung_Cancer), set up by Henschke, Yankelevitz, and top officials from WCMC, including Antonio Gotto, the dean of the medical school.

Though the announcement of the Liggett contribution appears in a press release, the origin of the funds as tobacco money is not disclosed in the group's papers.

The foundation supports research at multiple sites participating in the study and provides money to WCMC.

only 10 percent of informed consent forms, individuals involved in the review said.

• The reviewers asked for patient data files as well, but there is no evidence that these files have been provided.

"Recruitment of new subjects under the current protocol should be terminated and resources focused on the analysis and follow-up of subjects already enrolled," the review committee wrote. "We do not believe that accrual of additional subjects will substantially enhance the present conclusion (e.g. that CT screening can detect a substantial fraction of early stage cancers) or provide further strong evidence that such screening should be implemented as a matter of public policy."

The committee met at Weill Cornell Sept. 11-12, 2008, and produced a report on Oct. 7.

"Because only 10 percent of informed consents have been documented historically, the investigators should discuss with the WCRC IRB a potential plan for the event that some study subjects do not have valid informed consent on file," the review committee wrote.

If indeed the consent forms don't exist, this "potential plan" would have to include retraction of papers.

The plan, if Weill Cornell were to take the committee's advice, could also include notifying cancer centers and local hospitals worldwide, wherever patients have been put on I-ELCAP studies.

"That number—10 percent—came from the investigators; not from our count," said a member of the group, who spoke on condition that he wouldn't be identified by name. At the site visit, the leaders of the screening group didn't offer to round up the other 90 percent of informed consent forms, he said.

"Why wouldn't you at least send out a request saying we have to document that?" a committee member said. "Why wouldn't you do that if everything is legitimate? That's what I am so curious about."

Officials at community hospitals and cancer centers that put patients on CT screening trials say they are yet to be told about events at Weill Cornell. Even the fact that a review committee had been convened has yet to get out beyond the small circle of Weill Cornell officials.

Excerpted text of the document appears on p. 10.

Email correspondence obtained by The Cancer Letter shows that the outside experts asked to be informed about subsequent developments, but received no information after they produced the report.

On Nov. 3, 2008, Piantadosi asked a Weill Cornell official in charge of the review to keep him informed.

"It would be a big help to me (conceptually) to have some confidential follow-up on how this circumstance resolves/evolves and how our report is used," he wrote, sending copies of the email to the other three members of the group. "I don't want to put the Dean's Office in an uncomfortable position, but it would be helpful for my internal barometer to have some sense of resolution. Can you tell me if this is possible and when it might happen?"

In the email exchange, committee chair Rubin echoed Piantadosi's request.

August 2002

NCI initiates the National Lung Screening Trial, a randomized national trial involving more than 53,000 current and former heavy smokers, ages 55 to 74. It compared the effects of two screening procedures for lung cancer: low-dose helical CT and standard chest X-ray. (http://www.cancer.gov/clinicaltrials/noteworthy-trials/nlst)

2003

The Henschke/Yankelevitz program is renamed I-ELCAP, "I" for "international," to reflect its expansion.

Oct. 26, 2006

In a paper in The New England Journal of Medicine, the Henschke group reports that the 10-year survival of patients diagnosed with lung cancer after screening is 80 percent—but 92 percent for individuals diagnosed with stage I lung cancer and treated after screening. These two claims are based on two and one patient in folllow-up at 10 years, respectively.

The paper also claims that eight patients—found to have early stage lung cancer, but declined care—proceeded to die within five years. The paper doesn't state their causes of death, but in subsequent correspondence, Henschke states that these eight subjects died of lung cancer.

"You could prevent 80 percent of deaths [through screening]," Henschke repeats to the New York Times (http://nyti.ms/lG1PoF).

The Lung Cancer Alliance, a pro-screening patient group, argues that the finding should form the basis of changing the standard of care for current and former smokers by incorporating CT screening.

"I think it is fair to say that the entire committee is interested in this follow-up," he wrote later that day.

Responding to this email on Nov. 4, 2008, Mary Simmerling, assistant dean, research integrity, wrote:

"Geoff, David, Larry, and Steve,

"At this point I can provide you with only very preliminary follow-up. We are still in the process of reviewing the report you submitted. I expect that careful consideration of the issues raised in your report will take some time, as will deliberations by various institutional bodies about how best to proceed."

But committee members haven't heard any updates, sources said.

"Did they really find 40,000 consents, when they only ever audited 4,000, if they even did that?" a review committee member said. "I think if the answer to that is 'No,' that would partially explain why they squeezed Henschke out."

In January 2009, the institution ended its participation in the screening trial. In March, the Weill Cornell institutional review board rejected an application by Henschke and Yankelevitz to restart their screening protocols and asked for multiple changes to the protocol and consent document. The letter reflected the findings the review panel submitted confidentially six months earlier. There is no evidence that Henschke and Yankelevitz ever responded to the requested changes.

In January 2010, this publication reported that I-ELCAP has moved its "coordinating site" to the Arizona State University's Biodesign Institute in Tempe. Top leaders of the group—Henschke and Yankelevitz—have become clinical professors at Mt. Sinai School of Medicine (The Cancer Letter, Jan. 22, 2010).

The mechanics of the move raise questions about patient protection from research risk.

It's unclear whether the I-ELCAP coordinating center was under oversight of an IRB at the time of transition, which likely began when the study was stopped at WCMC in January 2009, and not restarted at ASU until many months later after WCMC rejected I-ELCAP's application for renewed IRB approval in March 2009.

There is no publically available information to suggest whether the group's activities stopped at any point in 2009 though, or if contributing sites, that were transmitting identifiable patient information to the I-ELCAP coordinating center, were notified that the study was no longer IRB approved and thus human subjects oversight was not in place.

"If they were indeed running a coordinating center and collecting patient data without IRB approval and oversight, that would be a major deviation from all U.S. and international requirements for performing clinical research," said Weiss.

After I-ELCAP moved its coordinating center to the Arizona State University BioDesign Institute, $491,850 in funds Henschke and Yankelevitz originally obtained from Liggett were transferred to the Biodesign Institute in the form of a cash grant to support "cancer research." This effectively closed out the Foundation for Early Lung

The conflict of interest disclosure statement on the paper reads that "no potential conflict of interest relevant to this article was reported." Doctors who answered simple questions based on the article were able to receive continuing medical education credits.

There was no mention of the funding received from the tobacco industry except a mention of the foundation.

Nov. 3, 2006

In a Q&A with The Cancer Letter, Henschke says she regards the NCI-sponsored National Lung Screening Trial as unethical, because it would randomize former and current smokers to the no-treatment arm. "I know that we couldn't do it here," Henschke said. "We couldn't participate, because we saw that the chest x-ray missed 85 percent of the early cases. I don't think that in New York State anybody participated."

Henschke made similar comments to other media outlets, contending that it was unethical to randomize subjects to chest X-ray screening as her study had already shown that CT screening was superior.

Nov. 22, 2006

The Cancer Letter publishes an internal I-ELCAP document titled "I-ELCAP Soundbites," instructing group investigators to spin their message. They are told to say that results published in NEJM present a "compelling" case for changing the standard of care to include CT screening of former and current smokers.

The soundbite sheet instructs investigators to obscure the nature of the I-ELCAP study design, avoiding the term 'observational', and to argue that

Cancer Detection which Henschke had set up with Cornell leadership to house the research support she was receiving from the Tobacco Industry.

In 2009 Henschke appeared to have set up a new foundation, called the Early Diagnosis and Treatment Research Foundation, which is where she asks donations to support her research to be sent from the I-ELCAP website. This foundation appears to be based in what appears to be a residential address in New York City.

The new foundation's leadership includes Alan Nelson, executive director of Biodesign Institute, tax documents show. The IRS 990 forms for the two foundations are posted at http://www.cancerletter.com/categories/documents.

"Not An Acceptable Standard"

Review committee member Carbone declined to comment on the report, but found it possible to discuss the underlying issues without drawing on materials covered by his confidentiality agreement with Cornell.

"I have known Claudia for years, and I have knowledge of the situation that's outside what we did for that report," Carbone said. "I also have no knowledge of what Cornell did in response to the report."

Carbone said that the National Lung Screening Trial showed a 20 percent relative drop in lung cancer mortality rates in former and current heavy smokers—so, at least directionally, I-ELCAP's conclusions were correct.

"There is a positive mortality effect of screening CTs in high-risk populations," he said. "But she was claiming specific numbers that certainly haven't been validated."

Asked whether it's common or appropriate for clinical trials coordinating sites to state that they are unable to produce documentation of consent, Carbone said no.

"That's not an acceptable standard for even an aspirin trial," Carbone said. "When you are talking about radiation, with potential risks, it's especially not acceptable."

Keeping documentation of informed consent is "one of the most fundamental aspects of protection of human subjects," Carbone said. If the forms can't be found, "it's an ethical problem."

Statistical design of the I-ELCAP cohort has been known to be a problem, Carbone said. "A lot of these studies were really not studies," he said. "They were observational cohorts, so they really didn't have sample size calculations. We knew that. I have been to I-ELCAP meetings. Claudia has invited me to present at her meetings, and I've seen the design of the protocol."

Vanderbilt didn't take part in the I-ELCAP study. Instead, it took part in NLST, a trial the I-ELCAP supporters and the Lung Cancer Alliance opposed.

Another member of the committee said that internal controls at Weill Cornell were "so loose as to be alarming."

The fact that the I-ELCAP structure was designed decades ago shouldn't be a factor, the committee member said.

CT screening for lung cancer would save healthcare dollars, even though publications from Henschke and colleagues suggest that it would not.

Oct. 8, 2007

A blog entry by the Wall Street Journal quotes Henschke and Yankelevitz, acknowledging that General Electric had licensed their technology sometime after 1999, and that the technology generates royalties.

Henschke and Yankelevitz state that NEJM was aware of this matter and found it irrelevant. Yankelevitz owns shares in and consults for PneumRx, a company that makes steerable lung biopsy needles.

The entry notes that GE funds the Lung Cancer Alliance, where Henschke serves as member of the scientific advisory board. A Henschke associate, James Mulshine, serves as a member of the LCA board.

Mulshine, associate provost for research at Rush University, later breaks embargo on a paper in which he played no part, as it suggested that CT screening may be beneficial. How Mulshine obtained the paper prior to publication is never uncovered, but it had been circulated confidentially within the NCI-funded CISNET group prior to publication (The Cancer Letter, June 6, 2008).

Jan. 18, 2008

Eight years after Henschke and Yankelevitz filed their first patent, The Cancer Letter reports that Henschke and other leaders of her group built an estate of 27 patent applications worldwide, covering technologies and methods of screening—and one U.S. patent that covers innovations in lung cancer screening, including:

"It was firmly anchored in earlier time, but not so much earlier that you could escape auditing, quality control and informed consent, and not so much earlier that you would think it was a good idea for 50,000 people to be accrued to an uncontrolled trial," he said. "And I am quite shocked to know that they went on and put 10,000 more patients on the study [after the committee issued its recommendation to stop accruing patients]"

Lessons of Medical History

"Throughout my career, I have had one overriding concern: to respect the lessons of medical research history," said Otis Brawley, chief medical officer of the American Cancer Society. Brawley, who has studied and written about ethics in medical research and screening, said, "It is possible to be well meaning, fail to learn the science and fail to ask simple questions and become complicit in tragedy."

Brawley oversees the ACS journals, including Cancer, which recently published an I-ELCAP paper in which disclosure of funding sources and conflicts of interest seemed discordant with previous disclosures. That article, like many others, says that all subjects signed consent forms.

"We were hearing about possible consent problems on the ELCAP and the many versions of it from news reporters and scientists in February," Brawley said in an email.

"Given the known inconsistencies surrounding the trial's previous publications and funding sources, these were legitimate questions that needed to be confirmed or refuted. I worry about our ethical responsibilities. We have a responsibility to assure appropriate action, if there are problems. The public has the right to and will ask us 'when were we told about it and what did we do about it?'"

Therefore, on March 8, Brawley approached the institutions employing the authors and asked a series of questions about the study. After Brawley's letters to the institutions went out, The Cancer Letter provided him with a copy of the Weill Cornell review committee report.

"We have to be fair to the investigators and have concern for the subjects in the study," Brawley said in an email. "Our first step regarding this report will be to approach the institutions again asking for a response to this report without pre-judgment."

Brawley was one of the two journal editors who called for an external audit of the I-ELCAP data in 2008 after noticing data inconsistencies in I-ELCAP publications. Bruce Chabner, editor-in-chief of The Oncologist, a journal that had published a Henschke paper, similarly called for audits.

After The Cancer Letter provided him with a copy of the report by the review committee, Chabner said the document demands a response by Henschke and Weill Cornell.

"This review is highly critical in some very important areas: consent and the lack of biostatistical framework for the trial," said Chabner, director of clinical research at the Massachusetts General Hospital Cancer Center and chair of the National Cancer Advisory

clinical trial methodology, software for interpreting scans, and the technology of biopsy needles.

None of these patents, pending or otherwise, had been reported in any of the group's publications.

March 14, 2008

The Cancer Letter reports Henschke's failures to disclose conflicts of interest—patent applications and consulting arrangements—in lectures that provided CME credit.

NEJM editors report that they were aware of the intellectual property held by the group, but found them irrelevant.

March 26, 2008

The Cancer Letter and The New York Times report that Henschke had received $3.6 million from Liggett, and the money was placed in a foundation run by the researchers and top officials of their institution.

In journal publications, this support wasn't listed as a contribution from Liggett, but as support from an independent foundation. The Times story is posted at: http://nyti.ms/atq161

March 2008

In a letter published in The Oncologist, Peter Bach, a pulmonologist and health systems researcher at Memorial Sloan-Kettering Cancer Center, suggests that several points made by Henschke—in a review paper regarding CT screening—are not supported by the references provided to support those assertions.

Board. "The fact that it's continuing indefinitely has no merit. I don't see how they can do that."

Clearly, the report required follow-up, which should have included notification to research sites and the public, Chabner said.

"What I wonder is, what happened to this report?" he said. "Why didn't something happen to follow up on it?"

Henschke's departure from Weill Cornell isn't enough, he said. "That's not really dealing with the problem," he said. "It's a serious problem if there is no biostatistics, and the consent is not handled appropriately, and if the trial just continues indefinitely.

"You can't justify that, because there is morbidity. The report really does demand a response on Cornell's part, and on Dr. Henschke's part. And if there isn't a satisfactory response, we will have to consider other action."

This could lead to retraction of papers, Chabner said.

"That's a possibility—absolutely," he said. "I will ask for a response from both the university and from the investigator. You have to give them a chance to answer."

The fact that the study continues to accrue patients, now under the auspices of the BioDesign Institute, is troubling, Chabner said.

"One of the issues here is if this study continues indefinitely, with people being CTed and biopsied and all the rest, there is risk to patients, and this can only be justified if there is an IRB-approved biostatistical reason to continue," he said. "If there is no biostatistical plan—and if there is no informed consent—then the whole thing is seriously flawed."

NCI Supported Research Meetings

Chabner declined to discuss the matter in his capacity as NCAB chair.

NCI played an important role in funding a Henschke trial, ELCAP, which led to a 1999 paper in The Lancet. The study was funded through NCI's investigator-initiated research grants, databases show.

The HHS grants database shows that from 1995 to 1998, Henschke was the principal investigator on the ELCAP study, where 1,000 persons at high risk for lung cancer were screened for pulmonary nodules, using both chest X-ray and low-dose helical CT (R01-CA-063393).

The Henschke, et al., paper in The Lancet states that researchers enrolled 1,000 symptom-free volunteers, aged 60 years or older, with at least 10 pack-years of cigarette smoking and no previous cancer.

The study found that CT screening was more sensitive than chest X-ray. Nodules were found in 233 volunteers who underwent CT, compared with 68 who got chest X-rays. According to Henschke and her followers, this finding made further randomization unethical. CT detected 27 cancers and chest X-ray detected seven.

Though I-ELCAP wasn't run in the same way as institute-funded cooperative groups, the project received some NCI funding.

Also, the institute chipped in for I-ELCAP semi-annual meetings, which allowed the group to display the institute's logo

March 2008

Henschke and Yankelevitz correct financial disclosures in JAMA to include the patent estate.

April 2008

Henschke corrects sources of funding in NEJM article. The journal's editors write an accompanying editorial, noting that:

"It is the responsibility of authors to disclose fully and appropriately the sources of funding of their studies. We expect that authors will be particularly attentive to transparency in reporting if a funding entity has a vested interest in the outcome. The public's trust in biomedical research depends on it." (http://www.nejm.org/doi/full/10.1056/NEJMe0802618.)

May 2008

The American Journal of Respiratory and Critical Care Medicine publishes a note from the editor in chief, correcting financial disclosures in an editorial by Henschke: http://ajrccm.atsjournals.org/cgi/reprint/178/5/542.

July 2008

Henschke reports that enrollment procedures, originally described in the group's 2006 NEJM paper, were not followed as described, but instead that some subjects diagnosed with lung cancer through screening were later removed from the analysis. The correction is posted at http://www.nejm.org/doi/full/10.1056/NEJMc086327.

Henschke also reports that five out of eight subjects—originally described as untreated despite having early-stage lung cancer—had, in fact, advanced lung cancer.

on meeting materials. Henschke's associate, Yankelevitz, received an R01 grant (R01-CA-78905) to develop a CT image database and related analysis tools.

The grant was independent of ELCAP and I-ELCAP, said NCI Deputy Director Doug Lowy. However, Lowy said the institute provided clinical supplements to the grant, to pay for follow-up for the 1,000 patients from the ELCAP cohort.

The ELCAP cohort was folded into the larger I-ELCAP cohort.

Yankelevitz was also part of a U01 collaborative grant, a consortium of five sites that worked to develop to a collection of CT images that has become the Lung Image Database Consortium (LIDC). This work was independent of ELCAP and I-ELCAP, Lowy said.

Lowy said he was unaware of the Weill Cornell review until it was brought to his attention by The Cancer Letter and The New York Times. The institute would look into the matter, he said.

In an email that was addressed to The New York Times reporter Gardiner Harris but also sent to The Cancer Letter, Henschke suggested that the surfacing of the confidential report is the latest in a series of challenges she is facing.

These include being deposed by attorneys representing tobacco companies in connection with a Massachusetts lawsuit, which seeks to provide CT screening as a component of compensation for future and current smokers in the state. I-ELCAP leaders have been engaged as expert witnesses by the plaintiffs.

"The context and timing of your questions concerns me," she wrote to Harris. "As you know, numerous I-ELCAP sites are currently fighting a subpoena by Philip Morris—a threat to lung cancer research across the board. I am scheduled to be deposed this week in connection with this legal action; my subpoena arrived one week before the NLST validated our findings.

"Awfully coincidental."

DISCLOSURE: ACS Chief Medical Officer Otis Brawley and The Cancer Letter Editor and Publisher Paul Goldberg are co-authors of an upcoming book about the U.S. health care system. The book is scheduled for publication by St. Martin's Press.

Weill Cornell Never Disclosed Findings: Lacking Consent, Design Flaws in I-ELCAP

In September 2008, Weill Cornell convened a four-member independent scientific review committee to focus on the International Early Lung Cancer Action Program, which had operated from that institution since 1992.

The committee was headed by Geoffrey Rubin, then-chief of cardiovascular imaging in Stanford University's Department of Radiology, now chair of the Department of Radiology at Duke University.

Group members were:

• David Carbone, the Harold L. Moses Chair in Cancer Research and director of Specialized Program of Research Excellence

July 2008

The Lancet publishes a correction to an earlier Henschke publication to note undisclosed financial conflicts of interest: http://download.thelancet.com/pdfs/journals/lancet/PIIS0140673608610739.pdf

Sept. 1, 2008

Peter Bach writes a follow-up letter in The Oncologist, arguing that Henshcke's "untreated" patient survival curve, previously published in that journal—which now included 13 subjects, up from eight in the earlier NEJM article—could not be correct due to the reported dates and reported censoring distribution.

Henschke responds that another five subjects—originally reported to have early lung cancer and not treated—were also misclassified.

This takes the number of patients labeled as having early lung cancer and dying within five years down from a total of 13 (eight in the NEJM paper, plus an additional five in the Oncologist), down to three.

In the same issue, Bruce Chabner, editor-in-chief of The Oncologist, calls for an audit of the data.

"I just don't know what the hell happened with this study," Chabner, clinical director of the Massachusetts General Hospital Cancer Center, tells The Cancer Letter. "The water has become increasingly murky, and God knows what's at the bottom of this. Unless the study is audited, it's not believable."

Sept. 11, 2008

A scientific review committee is convened by Weill Cornell to examine Henschke's work. The committee is headed by Geoffrey Rubin, then of Stanford University, and includes

in Lung Cancer at Vanderbilt-Ingram Cancer Center,

• Lawrence Goodman, professor of radiology and chief of thoracic imaging at the Medical College of Wisconsin, and

• Steven Piantadosi, director at the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai Medical Center.

Excerpted text of the group's report follows:

The outside review committee was asked to address 11 questions.

An excerpt from the committee report follows:

Antonio M. Gotto, [the Dean of the Medical College], has arranged for this external review of the scientific endeavors of Drs. Henschke and Yankelevitz. Scientific review of research programs is normal practice at academic research institutions, whether carried out internally or by external funding agencies.

This review is not a scientific misconduct investigation. We have every reason to believe that Drs. Henschke and Yankelevitz have conducted their research in a forthright, honorable, and transparent manner, consistent with accepted principles of science and academic inquiry. However, our belief does not necessarily make it so.

Therefore, we request that this external Committee of Scientific Review address the following matters during their deliberations, and document their findings in a final report:

1) Do the study design methodologies employed by Drs. Henschke and Yankelevitz conform to commonly accepted principles, and, if not, to what extent do the study design methodologies depart from these principles?

2) Do the proposed implementations of the studies undertaken by Drs. Henschke and Yankelevitz conform to commonly accepted principles, and if not, to what extent do the proposed implementations of the studies depart from these principles?

3) Do the actual implementations of the studies undertaken by Drs. Henschke and Yankelevitz meet their proposed implementation strategies, and if not, to what extent do they differ?

4) Have the data been collected in a manner consistent with commonly accepted principles of research integrity, and if not, is there any reason to conclude that the data have been collected inappropriately, altered, or incompletely considered in analyses?

5) Do the data analyses of the studies undertaken by Drs. Henschke and Yankelevitz conform to commonly accepted principles, and if not, to what extend do the data analyses depart from these principles?

6) Are the conclusions derived by Drs. Henschke and Yankelevitz, on the basis of their analyses of the available data, supported by commonly accepted scientific principles and practices, and consistent with conclusions that might be reasonably derived by researchers knowledgeable in this field of inquiry, and if not, to what extent are the conclusions not supported by these principles and practices, or divergent from conclusions that might be reasonably derived by knowledgeable researchers?

7) Do the computer algorithms employed in the analyses of the pulmonary lesions avoid systematic biases and design flaws, and

David Carbone, of Vanderbilt Ingram Cancer Center, Lawrence Goodman of the Medical College of Wisconsin, and Steven Piantadosi of Cedars-Sinai. Members of the committee receive $10,000 honoraria for the review and sign confidentiality agreements.

Sept. 23, 2008

American Cancer Society Chief Medical Officer Otis Brawley urges an audit of I-ELCAP data.

"I am very concerned about the I-ELCAP data and the I-ELCAP findings, and I can't justify using I-ELCAP at this time," says Brawley, at a meeting he called to consider pooling data from lung cancer prevention studies. "I think we can only use the I-ELCAP data if there is an external audit to verify that data, and there is an independent reanalysis of that data" (The Cancer Letter, Sept. 26, 2008).

Oct. 7, 2008

The external review committee finds that informed consent forms are present for only 10 percent of I-ELCAP patients, and that there is no common protocol, sample size calculation or plan to ever stop the study—and recommends that enrollment be ceased.

The committee also reccomends that the IRB convene to determine the next steps, if informed consent forms for enrolled subjects cannot be found.

Weill Cornell makes no public statements about this finding, and does not report to medical journals or the Office of Human Research Protection that they may have human subjects violations in the ongoing study.

The committee members, despite inquiries after their review, are never told about the outcome of their work.

if not, is there any reason to conclude that the algorithms include systematic biases or design flaws?

8) Since Drs. Henschke and Yankelevitz have conducted substantively similar research projects before and after the various financial interests (potential conflicts of interest) were present, have their study design methods, implementation strategies, data analyses, and/or results reporting been consistent during the time periods before and after the potential conflicts of interest existed, and if not, exactly how did these methods, strategies, analyses and reporting change?

9) With regard to the previous questions, if your review has revealed departures from normal and expected study design methods, implementation strategies, data analyses, and/or results reporting, is there any evidence that these differences were employed systematically to introduce bias into the outcomes in such a way as would benefit Drs. Henschke and Yankelevitz and/or the tobacco industry?

10) Based on your review of the published critiques of the work of Drs. Henschke and Yankelevitz and the responses of the investigators to such critiques, are there specific issues that you desire Drs. Henschke and Yankelevitz to address in writing after the on-site portion of your review?

11) Based on your review that you have undertaken of this body of work, please provide your opinion as to the merit of Drs. Henschke and Yankelevitz's continuing this line of scientific inquiry. If you conclude that there is value in the researchers continuing this line of scientific inquiry, please provide your suggestions for potential improvements in the design, implementation, data analyses, reporting, WCMC oversight, external oversight, and/or other infrastructure matters related to the research.

Scope of Review

The four reviewers decided to take a longitudinal view, encompassing the early studies and later spinoffs. Their review included ELCAP, NY-ELCAP and I-ELCAP cohort as well as the Flight Attendants Medical Research Institute study of passive smoking and the American Legacy Foundation-sponsored study of smoking cessation.

The review states: Planning and implementation of the subsequent NY-ELCAP and I-ELCAP trials followed a similar design as the original ELCAP.

Both were single-arm, multi-center trials, providing an opportunity to observe the frequency and character of initial (prevalent) and interval (incident) lung nodules, including those nodules ultimately proven to be lung cancers.

Subjects with proven lung cancer are intended to be actively followed to assess survival or lung cancer curability. Subjects without proven lung cancer are not intended to be actively followed.

As of the time of this review, close to 40,000 subjects have been recruited into the I-ELCAP trial across 38 centers both within and outside of the United States.

Despite the strengths of the program and the value of the data

Jan. 9, 2009

The Cancer Letter reports that the NEJM is sanctioned by the Accreditation Council for Continuing Medical Education for failure to disclose conflicts of interest on the part of I-ELCAP investigators. The journal has to change its procedures for monitoring conflicts. The Times covers the story: http://nyti.ms/jcAQ39.

Early 2009

I-ELCAP protocol at WCMC expires and is not renewed after the IRB rejects the application for approval, sources say.

Basic elements of an acceptable protocol are lacking, including a sample size calculation. Informed consent reportedly doesn't offer alternatives, such as foregoing screening.

The document also doesn't disclose the investigators' financial conflicts of interest.

The Weill Cornell IRB writes a letter to Henschke based on the Oct. 7, 2008 external committee report, instructing Henschke to provide extensive documentation on informed consent and correct multiple problems, including that the informed consent form states that "CT screening is NOT experimental," and that the protocol contains no sample size calculation.

It's not clear whether Henschke ever responded to any of these requests.

Henschke is told by WCMC officials to notify participating sites that the I-ELCAP protocol is no longer open, but it is not clear whether outside sites were ever notified that they were submitting data to a study that had been closed because of protocol problems.

collected by I-ELCAP, the Committee has a number of important concerns about the program as follows:

A. The I-ELCAP investigators have published papers and editorials that explicitly state or strongly imply that their data indicate that CT screening for lung cancer is both cost effective and definitive (sufficiently proven) to support public policy decisions in favor of widespread lung cancer screening.

1. The Review Committee does not consider this conclusion supportable, because without a control group in I-ELCAP, it is impossible to know if the impressive lung cancer survival and curability rates reported for screen detected cases are a result of over-diagnosis and length-time biases.

2. The conclusion is also not supportable because the full cost of screening is not measurable without tracking all subjects and measuring the cost of screening subjects who did not have lung cancer. These costs most importantly include the financial expense, morbidity, and mortality of secondary interventions (imaging tests and surgical procedures), but also include the psychological stress associated with following lesions ultimately determined to be benign.

3. Screening necessitates multiple CT scans in a sizable proportion of the population. Although the radiation risks for the individual are low, population risk can and should be assessed.

4. Published criticisms in the scientific literature regarding the absence of a control arm, the lack of assessment of the cost of intervention in the screened population, and concerns about the potential for over-diagnosis and length-time biases have been treated dismissively and defensively by the IELCAP investigators. Although apparently disputed, one usually reliable source quoted the investigator(s) suggesting that a randomized controlled trial such as the NLST is unethical based on the existing data. The absence of public recognition of shortcomings in their study design has created an adversarial relationship with key investigators in the field, hindering productive discussion and creating an environment with little external input into the trial.

B. In contrast to current accepted practices of clinical trial design, I-ELCAP lacks

1. Standardized patient eligibility criteria across sites.

2. A target sample size based on achieving the primary statistical goal of the trial. As a result there is no definitive end to the trial, and it is perhaps more accurately referred to as a registry than a trial.

3. Independent data management, quality control, and oversight structures

4. Positive confirmation of valid informed consent for all subjects at all sites by the coordinating center

5. Formalized site audits with pre-defined procedures for conducting the audits with standardized and enduring reports and written corrective action plans.

C. There are insufficient real-time data reporting and analytical tools to manage effectively and derive full scientific benefit from the substantial amount of data collected in the 40,000 subjects.

The current customized software tool, while apparently

July 2009

Weill Cornell sends out a letter notifying the I-ELCAP sites that the coordinating center would move to Arizona State University's Biodesign Institute. Weill Cornell's name is removed from the I-ELCAP website.

August 2009

The sum of $491,850—originally obtained from Liggett is transferred to a foundation in Arizona. Alan Nelson, the Bioesign institute's executive director, joins the board of another Henschke foundation.

Late 2009

Henschke and Yankelevitz are appointed adjunct faculty at the Biodesign Institute. No public announcement is made.

Jan. 22, 2010

The Cancer Letter reports that I-ELCAP has moved its "coordinating site" to the Biodesign Institute. Top leaders of the group—Henschke and Yankelevitz—become clinical professors at Mt. Sinai School of Medicine.

Nov. 4, 2010

The NLST on lung cancer mortality found 20 percent fewer lung cancer deaths among trial participants screened with low-dose helical CT.

In multiple press interviews, Henschke claims that the NLST has confirmed what her study found, and that the study meant that 80 percent of lung cancer deaths could be avoided with additional screens (http://nyti.ms/aOGQVm).

Publication of a paper containing the trial's results is expected in the next few months. It's unclear how the NLST findings would translate into health policy (The Cancer Letter, Nov. 26, 2010).

allowing effective data capture, does not provide for flexible queries in real time across all study sites that might be important for effective monitoring of the trial and assuring data quality.

D. Regular input from an informed independent external scientific advisory board for vetting both strategic and tactical issues is lacking. Enduring reports from the external advisory board are mandatory.

E. Given the global reach of this program, its potential for advancing the state of the art in early lung cancer detection and treatment, and its potential economic and political impact, it is surprising that the WCMC administration has avoided direct oversight of this program, especially knowing that scientific controversy has surrounded I-ELCAP almost from its inception.

Committee Recommendations

The Review Committee was presented with a list of 11 specific charges, which we have coalesced into eight topic areas, addressed explicitly as follows:

A. The study methods and implementation conform to commonly accepted principles for an observational study with the exception of the aforementioned limitations relating to consistent entry criteria, pre-defined trial end, formal data management and oversight procedures, insufficient documentation of site audits, and central confirmation of valid informed consent for all subjects.

B. The data collection and analysis have generally conformed to commonly accepted principles, and there is no evidence to suggest that data have been altered or maliciously misreported. There has been selective collection of information on cancer cases (by design) as opposed to cases in which the intervention proved the nodule to be benign. As previously discussed, substantial improvements in the infrastructure to support data collection and analysis would provide tighter oversight over the conduct of the trial and should yield many important and presently unreported insights, particularly relating to the participants without documented lung cancer.

C. In general, conclusions derived from the investigations are appropriate and reasonable for an observational trial. However, there do seem to be overstatements that cannot be fully supported by uncontrolled data. While some publications from the I-ELCAP team have specifically stated that the I-ELCAP data justify the implementation of lung cancer screening, Drs. Henschke and Yankelevitz stated unequivocally to the Review Committee that they did not believe that their data provide definitive evidence that screening for lung cancer should be implemented as public policy.

D. No systematic biases or design flaws were evident in the computer algorithms developed to analyze pulmonary lesions.

E. No temporal trends in the research design, implementation, or conclusions reached were evident as a result of, or in association with, variations in funding sources.

F. The Review Committee did not find evidence to suggest that the study design, implementation strategies, data analyses, or results reporting were biased to benefit either Dr. Henschke or Yankelevitz personally or the tobacco industry. Changes in the study design and implementation appear to be based exclusively on iterative technical improvements and incorporation of new knowledge. Because of the potential appearance of conflict of interest due to tobacco funding, the source should have been acknowledged in all publications. Simply listing the foundation "Vector Fund" obscures the source and gives the appearance of impropriety.

G. The Committee does not require additional information from Drs. Henschke and Yankelevitz. However we do recommend preparation and submission of a summary document on the I-ELCAP accomplishments, future directions, context of conclusions reached relative to other published and ongoing trials of CT for the detection of lung cancer, as described in the subsequent section.

H. The Review Committee believes that the substantial body of work undertaken by Drs. Henschke and Yankelevitz is of sufficient importance that it should continue. Specific recommendations for continuing this work are provided in the following section.

Recommendations for Continuation

As stated above, the work of Drs. Henschke and Yankelevitz, particularly through the IELCAP have produced a valuable study cohort and international research team with the potential to answer many unresolved questions relating to the natural history of lung cancer, lung cancer curability, character and natural history of other pulmonary and extrapulmonary thoracic and cardiovascular disease in cigarette smokers, and risks and costs associated with interventions performed in screened subjects with benign abnormalities. To facilitate and enhance the quality of these important investigations, the Review Committee has the following recommendations:

A. Recruitment of new subjects under the current

protocol should be terminated and resources focused on the analysis and follow-up of subjects already enrolled. We do not believe that accrual of additional subjects will substantially enhance the present conclusions (e.g., that CT screening can detect a substantial fraction of early stage lung cancers) or provide further strong evidence that such screening should be implemented as a matter of public policy. Our opinion (and evidently that of the investigators) is that such a recommendation would follow only from controlled studies.

B. Pre-existing research commitments to FAMRI and the American Legacy Fund should proceed to a clearly defined completion.

C. The Review Committee is aware of, and respectful of, legitimate scientific debate and differences of opinion regarding the complex issues surrounding screening, public policy, and study design and interpretation. At the same time, the Review Committee recognizes an insular minority view adopted by the I-ELCAP regarding the scientific value/need for screening controls. Specifically, the investigators have adopted the philosophy that "a control group is unnecessary in diagnostic research", a view largely promulgated by one member of the research team. This issue is central to the I-ELCAP study design and debate about the overall value and validity of the results, and partly fuels acrimony in the public discussion.

The Review Committee recognizes the destructive potential of this view in this circumstance, and particularly when the diagnostic conclusions are used in support of public policy changes. The problem is not derived as much from philosophical differences as it is from I-ELCAP investigators' refusal to recognize their own fragile position and respect the contrary point of view. That view, embracing the need for a control group, currently drives the peer reviewed NIH sponsored screening trial and is widely acknowledged to be a key in providing the most reliable scientific evidence for guiding public policy.

Dr. Henschke and Dr. Yankelevitz have also acknowledged its value in their discussion with the Review Committee. We see the lack of balance in the scientific perspective taken by I-ELCAP on this issue as being damaging to the study and to the larger debate. The Review Committee therefore recommends that WCMC assist the I-ELCAP investigators in modernizing and rounding out its expertise on such methodologic issues by engaging appropriate internationally recognized experts. The Review Committee's explicit recommendations on this point are:

1. There is no value in fostering internal I-ELCAP "debate" on this point that would further entrench the current thinking;

2. I-ELCAP needs fresh senior methodologists to articulate a more mainstream scientific perspective and balance its historical view;

3. The design of new studies in this collaboration must show a record of appropriate deliberation on this and similar methodologic points, and acceptance of criticism, if the scientific reputation of I-ELCAP and WCMC is to be maintained.

D. Members of the scientific community are sufficiently concerned about recently reported and subsequently modified I-ELCAP data to call publicly for an audit of I-ELCAP results. In fact, such audits are an accepted part of all clinical investigations, and particularly for those trials with significant potential practice implications. For the purpose of considering this question and for determining the future direction and management of I-ELCAP, the WCMC and I-ELCAP should create and charge an independent external Scientific Oversight Committee as follows:

1. Current I-ELCAP investigators should not serve on the committee.

2. Membership should include but not be limited to: an NCI-representative, a thoracic radiologist, a pulmonologist, a thoracic surgeon, a pathologist, a clinical trialist, and a biostatistician. Optional, but potentially beneficial, would be the involvement of an epidemiologist and informatics expert.

3. The committee should convene at least annually and produce a formal report with recommendations to the Dean of WCMC and the principal investigators of I-ELCAP.

4. A formal charter, with committee members appointed under that charter, should define the charge of the committee.

5. The charge to the committee should include but not be limited to review of: the strategic plan for the program, ongoing operations and management of the trial, and study designs and analyses.

6. The committee should have fund raising and development activities in support of this program

explicitly excluded from its charter. However, all fund raising and disbursements should be transparent to the committee and WCMC.

E. The informatics support and in particular the data collection interface, data storage, and data reporting mechanisms should be revamped to meet current standards for data management of a 40,000-subject trial. Additional institutional resources will be necessary to support this initiative. An informatics expert with direct experience in building databases for large clinical trials should prepare the specifications and oversee implementation.

F. Improve auditing of data and data collection procedures at external study sites, also likely requiring additional resources, to include:

1. One hundred percent capture of valid informed consent. Copies (electronic or paper) of all consent forms should be sent to the coordinating center. Because only 10% of informed consents have been documented historically, the investigators should discuss with the WCMC IRB a potential plan for the event that some study subjects do not have valid informed consent on file.

2. Compliance with data reporting accuracy and completeness.

Independent Scientific Review Committee Report

3. Regular, formal compliance audits of all sites in the style of cooperative oncology groups should be performed with written records of the audit stored at the coordinating center, along with specific corrective action plans.

G. Make the database of CT images, histology specimens, and subject characteristics publicly available to other investigators. The database, hosted by WCMC would be an invaluable resource for future scientific and training of CT interpretation, and would reflect well both on the investigators and WCMC.

H. While the potential investigations using the I-ELCAP dataset are innumerable, the Committee recommends the investigation and reporting of the following:

1. Actively ascertain, from at least a large representative sample, any and all interventions resulting from I-ELCAP screening. This will require additional data collection. This should specifically and separately include a complete analysis and report of the frequency and outcomes of image guided procedures and futile thoracotomies performed in the work-up of CT-detected lung findings. In a subset of patients, additional costs – such as additional imaging (CT, PET), office visits, and lab tests – should be ascertained to determine the true costs of screening.

2. Propose and implement methods to assess the extent of over-diagnosis in the CT detection of lung cancer.

3. Assess the relationship between lesion size and curability.

4. Other valuable analyses that should be considered include the impact of variations in image interpretation approaches, image acquisition techniques, risk profiling, and image processing techniques in the CT detection of lung cancer.

I. Encourage the network of investigators to continue and enhance collaboration to address new research questions, uniquely suited to this large consortium.

J. Prepare and publish a summary statement that I-ELCAP data are not compelling evidence that national healthcare policy should be altered and do not make the conduct of a randomized control trial unnecessary or unethical. Indicate the role of I-ELCAP in providing future knowledge and summarize the knowledge gained.

Emails to The Times: Henschke Offers Her Version of Events

Claudia Henschke, the leader of the International Early Lung Cancer Action Program, provided the following responses to questions from The New York Times reporter Gardiner Harris.

Henschke's publicist, Emily Flynn, of Podesta Group, provided these answers—contained in two emails—to The Cancer Letter.

The text of Henschke's responses follows:

Email 1: "Awfully Coincidental"

Gardiner,

I appreciated receiving your questions. The bottom line here is that I-ELCAP is a non-federally funded academic consortium of independent, autonomous sites that share certain data.

Accountability and responsibility for human protection lie at the local level. Our research focuses on the aggregate data. Ownership of the data is at the institutional level. The idea that we need to act as if we are an NCI cooperative cancer network that focuses on federally funded randomized treatment trials reflects a lack of understanding of non-federally funded research.

To answer your questions: First, yes, every site is required to get their own consent forms. We, while at Weill Cornell, got consents from all of our research subjects. Second, I don't know what "audit committee"

you are referring to, but none of the reviews of which I am aware has identified problems with our screening protocol.

Additionally, the I-ELCAP protocol was not suspended; we opted to move to a new IRB for the data pooling and we notified each of the sites of the change to the new IRB at ASU.

The study continues to recruit new patients.

The context and timing of your questions concerns me. As you know, numerous I-ELCAP sites are currently fighting a subpoena by Philip Morris - a threat to lung cancer research across the board. I am scheduled to be deposed this week in connection with this legal action; my subpoena arrived one week before the NLST validated our findings. Awfully coincidental.

If we are forced to hand over our raw data, the chilling effect on research generally and our studies specifically would be profound; and think about the precedent it would set. Turning over this data—when people continue to be screened—would constitute an enormous betrayal of the voluntary participants and the screening sites.

This is the story you should be writing: how big tobacco is trying to get its hands on confidential patient information and strip researchers of their academic freedoms. Instead, it appears that you and Otis Brawley of the American Cancer Society (whose soon-to-be-released book warrants a close look at his motivations, no?) are attempting to exacerbate these threats from big tobacco and even help Philip Morris with its case.

This is a historic time for lung cancer screening research. Rather than support those interests that seek to divide the research and patient community and further delay scientific progress, we should be working together to defeat a disease that kills far too many Americans.

My fellow researchers and I stand by our work, as do the thousands of lung cancer patients whose lives have been saved thanks to CT scans. I hope you can understand where I am coming from.

—Claudia

Email 2: "Unforeseen Problems"

Gardiner,

It would appear that my efforts to provide complete disclosure have created unforeseen problems and questions and that those who have been providing you with information are themselves either uninformed or intentionally trying to muddle the issues.

I have always worked on the assumption that the medical professionals knew the history of I-ELCAP and how it functioned. Therefore, I hope that the following is explanatory.

1. I-ELCAP was conceived as a prospective pooling program rather than performing a meta-analysis after various studies are done. This distinction was extensively discussed in the initial International Conferences on Screening for Lung Cancer. It was recommended that pooling in advance was much preferable to later meta-analysis. To that end, the participants in the Conferences requested that we prepare a protocol for pooling, which was unanimously accepted. There are many types of studies that pool or use data from previously conducted studies under their own IRBs. Such data pooling or modeling studies are not required to review or obtain the consent forms of participants to report the data

2. The I-ELCAP pooling effort has never received federal funds.

3. Some of the collaborating institutions received federal funding for their screening research. They voluntarily contribute to I-ELCAP and are free to publish the results from their projects independently. These federally funded grants were grants for specific screening projects, each with their own IRB, not for the pooling of the data which has its own IRB approval. I-ELCAP functioned with its own separate and distinct IRB, distinct from the individual screening site IRBs. I-ELCAP is also distinct from the Weill Cornell screening IRB (ELCAP which ended in January 2009).

4. Each collaborating institution has its own separate IRB.

5. I-ELCAP never had the responsibility of obtaining consents from participating patients.

6. The responsibility for obtaining consents rested with the individual researchers at each of the collaborating sites. The individual sites validated the consents had been obtained and that all the requirements of the I-ELCAP IRB were met.

7. In articles, to make a full disclosure, we included all the funding for the individual screening sites as they were responsible for their own funding. This information was provided to us by the individual sites.

8. In the article readers were advised that consents were obtained from all of the participants. This information was provided by the individual sites.

9. All site investigators were responsible for obtaining the consents locally and for following their local IRB process. We followed all the processes required by the IRB for the pooling effort and for its reporting. Our only requirement is to rely on their representation.

You assume you know better than 60+ IRBs as

to what is required for I-ELCAP collaboration. Your background in FDA exposes you to some forms of trials, but not all types.

Other people's background exposes them to oncology or surgical trials to obtain FDA approval. There are distinct categories of trials, both in terms of the extent of risk to the person and other regulatory requirements.

With regards to your questions about a "scientific review," yes, I remember participating in a scientific review process but not an "audit" as your original series of questions asked. Any review is confidential and I have agreed to confidentiality.

It is apparent that others who entered into the same confidentiality agreement have seen fit to betray confidences and their obligations. I have requested release from Weill Cornell of my confidentiality agreement so as to be better able to respond but will not answer your questions until Weill Cornell permits me to do so.

To address your questions about tobacco funding and now the subpoena, I first want to say how alarmed I am that the New York Times is apparently planning to put out a story about my research on or around the very same day that I am giving a deposition to Phillip Morris in response to an incredibly aggressive third-party subpoena with massive implications to academia. Given the timing of your proposed article and tone of your questions,

I am left wondering about your underlying agenda.

My feelings aside, let's set the record straight. Your implication seems to be that we were once aligned with big tobacco; that's absurd. When Weill Cornell accepted the unrestricted gift (not a grant) from Ben LeBow [chairman of the board of Vector Group, a holding company that owns Liggett, and recently named CEO of Borders, a bookseller], it was accepted at the suggestion of the advocacy and tobacco control community during the time shortly after the master settlement agreement when there was great concern that the monies were not being used to help those who had suffered the most – smokers and former smokers.

Liggett had previously broken ranks with the other tobacco companies and they decided to put in the initial funding for the large scale research program. The monies given to Weill Cornell were then placed in a foundation with oversight by senior Cornell officials.

The source of funding for the foundation was declared in a press release, and, despite their arguing a decade after we had received that funding that they did not know about it, the American Cancer Society commented about the announcement in a USA Today article on Dec. 4, 2000.

The monies were given with the parameters that tobacco would not be able to have any access to or limitation on the use of the funds or the publications.

They also were not to have any benefit from having made the gift. It was fully reported to Cornell's conflicts board as well as their legal affairs department for them to review and advice on reporting.

At that time, there was indeed hope that tobacco would stop their deceptive ways and try to cooperate with the public health community to help those who had suffered the most and were at greatest risk.

The unrestricted gift came from the Vector Group, the holding company of Liggett Tobacco, Inc. The gift was part of an effort by Liggett to get all of the cigarette manufacturers to fund research for early detection of lung cancer. Phillip Morris and the other manufacturers never agreed to participate and disagreed with Liggett on this issue as they did on many other issues.

I am not in a position to know the current motivation of Philip Morris, but I do know that the company is facing multiple class action lawsuits that could potentially cost them hundreds of millions of dollars. I-ELCAP results, among other research results, are being used by plaintiffs as part of their basis for requesting medical monitoring.

My colleague David Yankelevitz and I are not parties in that lawsuit. We have been subjected to a highly intrusive third-party subpoena that requests that all of our data as well as any correspondence relating to screening be turned over. It is an all-out assault on academic freedom with the potential to destroy the only large scale, ongoing screening research program in the US.

It would be a massive betrayal of the sites as well as the screening participants for us to be forced to turn over their data. Imagine how a participant who is still enrolled in the study would feel to learn that the data they contributed because of concern about lung cancer, or having lost a loved one to lung cancer, is now being used to defend the industry that likely caused the disease. How could they continue to participate in the study? How would any of the sites continue to participate, especially since I-ELCAP does not own their data?

The potential for massive companies to destroy academic research just because they do not like the results has enormous implications for society.

Here, Philip Morris, simply by use of invasive subpoenas would in essence destroy an ongoing research collaboration that now stands to contribute some of its

most important results to answer the still outstanding questions that are being raised about screening. Our future work now gains even more relevance in light of the results of NLST.

In response to the additional questions you sent, please see the bullets above. Weill Cornell performed screening under its own IRB (the ELCAP study) and it also contributed data to I-ELCAP research.

When the ELCAP IRB for the screening at Weill Cornell ended, participants at Weill Cornell were no longer recruited. I-ELCAP never functioned without having appropriate IRB approval and there was no gap.

I hope this sets the record straight.

—Claudia

Guest Editorial:

Patients In I-ELCAP Study Required Data and Safety Board Protection

(Continued from page 1)

Cornell, and then apparently the relocation of the principal investigators to other institutions in New York City and Arizona.

My comments are based on my experience with the construct of protocols, conduct of clinical trials, patient consent requirements, IRB oversight requirements and data auditing. They do not necessarily reflect the opinions of my colleagues or the institutions where I practice medicine or participate in teaching and research activities.

Although the I-ELCAP investigators have stated in their publications and editorials that their data demonstrate that chest CT scanning for lung cancer is of established value, the review committee pointed out some weaknesses in the study—the full population of subjects screened was not followed, nor were the costs of screening for those without lung cancer measured

One would assume the investigators might consider addressing these weaknesses with changes in the study methods—and/or developing means of collecting additional data on the subjects already enrolled— rather than continuing to accrue more subjects, as seems to be the case. At least this point was true at the time of the review committee evaluation.

What purpose is served by accruing more subjects? I thought their conclusion—that CT screening had value in diagnosing lung cancer earlier—had been reached; even published by I-ELCAP investigators in the Oct. 26, 2006, issue in the New England Journal of Medicine.

The review committee stated that the study has no target sample size, and as a result there is no definitive end to the trial.

A clinical trial with no end?

Ridiculous!

No such trial would ever be endorsed by peer reviewers and would never be approved by any of the cooperative groups themselves—and certainly not by NCI staff overseeing the conduct and funding of such a trial.

What is the endpoint?

The review committee indicated that the trial has no "standardized patient eligibility criteria across sites." From the I-ELCAP website several years ago, I obtained a copy of the protocol, dated Dec. 5, 2007. It is only 12 pages long.

In contrast, most cancer-related clinical trial protocols contain 100 or more pages, and are very detailed. The I-ELCAP protocol lacks clearly stated Eligibility Criteria, for example. There is no section delineating the statistical methods for analysis. There is no defined system of data submission, with time points and required information. And there is no definition of follow-up information collection.

Each participating institution is "free to choose the timing of repeat screening anywhere between 6-18 months." This is unheard of in cooperative group studies. Although there is freedom to choose the repeat screening interval, there is no specified number of repeat screenings—is it once, twice, or annually until further notice?

Every aspect of the study should be standardized at all sites, with specific requirements regarding the information to be collected and submitted, detailing when and how often. The review committee commented that the trial is "perhaps more accurately referred to as a registry than a trial."

The protocol does define, in detail, methods for CT image production, reading and assessment of nodule growth—but the whole document is indeed more compatible with a registry study, rather than a prospective clinical trial.

The current procedure for any clinical trial involving large numbers of patients or healthy subjects is to have a Data Monitoring and Safety Committee, comprised of peers uninvolved in the study, to review the data periodically (e.g., once every six months), ensuring the safety of the enrollees.

Such a committee also advises investigators when the study has reached sufficient accrual to stop the trial. The RC stated that no such committee existed, and that "enduring reports from the [an] external advisory board

are mandatory." I assume that no such advisory board has been established, per the 2008 RC recommendation that such was "mandatory."

If healthy people are still being enrolled without the establishment of an oversight committee or board, then that is a major deviation from standard procedures.

The RC stated the study lacks "formalized site audits with predefined procedures" and report generation. I would doubt the study leaders have any idea what is happening at the 37 participating sites besides their own.

Are the data being submitted valid? Are there sites failing to follow the protocol requirements? Have there been any actions by the study leaders to pressure deficient sites to improve? And even more importantly, are the leaders even aware if any sites are not doing good work?

I suspect not.

The RC made a list of 10 major recommendations for improving the construct and the conduct of this trial, some of which have up to six subheadings. All are worthwhile, and based on the RC members' expertise and experience with such studies.

Have any of these recommendations been implemented by the study leaders? Have the participating sites even seen these recommendations?

I suspect not, since the review committee's report was labeled "confidential."

If the Weill Cornell administration spent the money and time to invoke the services of such a committee, why has there been no oversight to ensure the recommendations are implemented? It appears the work of the review committee served no purpose. The report seems to have been filed away at Weill Cornell; forgotten when the two PIs left the institution.

Federal Document Title 45 CFR for Protection of Human Research Subjects requires the following: "Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval."

Did the Weill Cornell IRB notify the Office for Protection of Research Risks about the problems with this study, enumerated by the review committee?

I suspect not.

Did the Weill Cornell IRB notify OPRR when they suspended the study?

I suspect not.

The RC report states that "only 10 percent of informed consents have been documented historically." There is no requirement that the study center must retain a copy of the signed consent. However, the signed consent forms must be readily available at the other 37 centers.

Did the PIs ever check to ensure such records of consent were being kept at the other sites?

In a recent publication, the investigators state that "all participants gave informed consent under IRB-approved protocols at their respective institutions." (Henschke CI, et al: Assessment of lung-cancer mortality reduction from CT screening. Lung Cancer 2011;71:328-32.)

How would the PIs know that "all participants" signed a consent form approved by the local IRBs? Since there were never any on-site audits of the other centers, it is unlikely anyone knows whether or not all participating sites adhered to the mandatory requirements of consent-form signing and retention.

Although not addressed by the review committee, it is unlikely that the PIs ever sought to ensure that the IRBs at other sites had truly reviewed and approved the protocol.

I do not know if the protocol was ever amended. If it was, was there ever documentation that the local IRBs had reviewed and approved such amendments, as required by federal and international standards?

This study has multiple flaws—and the review committee pointed out these flaws in detail—yet there is no evidence that any of the RC's recommendations resulted in any action, except apparently to cause the relocation of the PIs from Weill Cornell.

How has the Weill Cornell IRB handled the PIs' failures to address these questions and problems?

Have the OPRR, the NCI officials handling the R01 funding, and the various journals that have published their work all been notified of the deficiencies in the study construct? Are they aware of the apparent lack of informed consent and the lack of oversight at the other participating sites?

I suspect not.

Weiss is a clinical professor of medicine at Georgetown University Medical Center and a oncology consultant to several oncology centers in the Washington area.

He is the former chair of the Data Audit Committee of the Cancer & Leukemia Group B. He served in that position from 1981 to 2007, personally performing hundreds of data audits. In addition, he has done numerous audits for other federal agencies, pharmaceutical companies and individual institutions.